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Treatment of idiopathic inflammatory myositis associated interstitial lung disease: A systematic review and meta-analysis

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ABSTRACT

Objective: Interstitial lung disease (ILD) is the most severe complication of idiopathic inflammatory myositis (IIM), resulting in significant increase in morbidity and mortality and for which the best treatment remains controversial. We conducted a meta-analysis to evaluate the efficacy of therapies used for the management of IIM-related ILD.

Methods: Studies were selected from MEDLINE up to July 2017. Two investigators independently extracted data on study design, patient characteristics, clinical features, treatment, follow-up and outcomes. Global survival rates and objectively confirmed lung function improvements were extracted as the main outcome for rapidly progressive IIM-related ILD (RP-ILD) and chronic forms of ILD (C-ILD), respectively, and pooled using the weighted mean proportion with fixed or random-effects models in case of significant heterogeneity ($I^2 > 50\%$).

Results: Twenty-seven studies encompassing 553 patients (male: 30.5%, age: 53.5 ± 5.5 years) were included in the meta-analysis. Globally, retrieved studies were of limited methodological quality (no controlled studies and only 2 prospective studies). Dermatomyositis (40%) and anti-tRNA synthetase syndrome (45%) were the most represented IIM subtypes. In C-ILD, functional improvement rates were 89.2% (95%CI 82.5–93.6; 7 studies, $n = 124$) for corticosteroids alone, 80.7% (95%CI 49.6–94; 6 studies, $n = 38$) for cyclosporine A, 64.1% (95%CI 46.3–78.7; 4 studies, $n = 32$) for azathioprine, 86.2% (95%CI 61.5–96; 2 studies, $n = 23$) for tacrolimus, 56.4% (95%CI 44–68.0; 8 studies, $n = 71$) for cyclophosphamide, and 76.6% (95%CI 50.4–96.0; 2 studies, $n = 20$) for rituximab. In RP-ILD, survival rates at 3 months were 51.7% (95%CI 24.2–78.1; 2 studies, $n = 11$) for corticosteroids alone, 69.2% (95%CI 55.0–80.5; 8 studies, $n = 146$) for cyclosporine A and 72.4% (95%CI 6.4–99.0, 2 studies, $n = 16$) for cyclophosphamide.

Conclusion: Despite aggressive immunosuppressive therapies, the short-term mortality of RP-ILD remains high. While immunosuppressive therapies are associated with significant functional improvements in most patients with C-ILD, substantial uncertainty remains about the best treatment strategy in the absence of good quality evidence.

1. Introduction

Idiopathic inflammatory myopathies or myositis (IIM) is a group of rare autoimmune diseases characterized by muscular involvement leading to muscle destruction, and frequent extramuscular signs such as arthritis, Raynaud's phenomenon, mechanic's hands and interstitial lung disease (ILD) [1]. Peter and Bohan's criteria of IIM historically distinguished polymyositis, dermatomyositis and overlap myositis [2,3]. Recent advances in immunology identified specific entities based on myositis-specific auto-antibodies and more precisely defined the broad spectrum of IIM [4]. Amongst extramuscular complications of IIM, ILD is both the most frequent and severe involvement, resulting in

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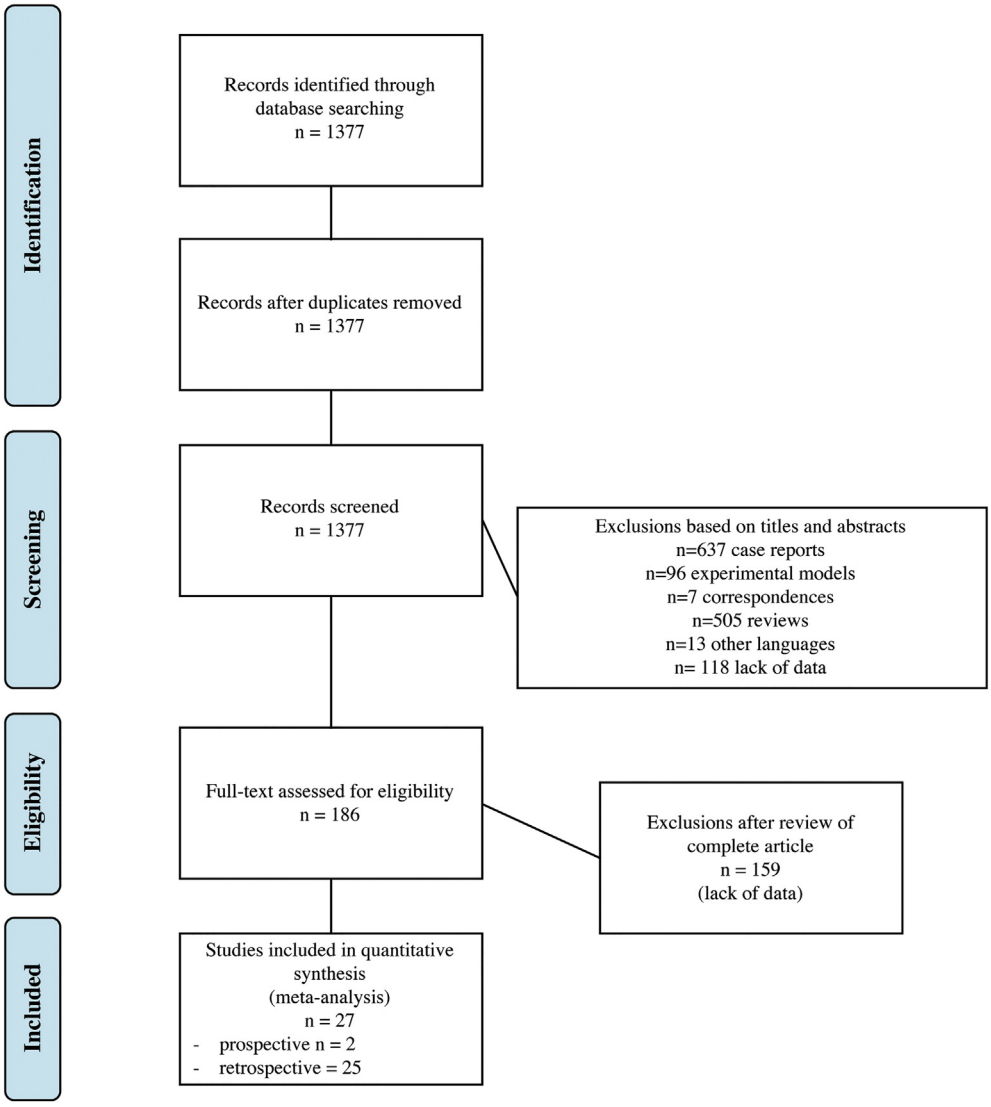

Fig. 1. Flow diagram.

a significant increase in mortality [5,6]. Therefore, the evaluation of ILD is crucial in the management of IIM, particularly in the anti-tRNA synthetase syndrome [4,7], anti-MDA5 [8], and anti-PM/Scl antibodies-associated myositis in which ILD is highly prevalent [7,9–11].

Myositis-related ILD encompasses heterogeneous entities that can be divided into two main clinical patterns depending of the disease course: chronic (C-ILD) and rapidly progressive (RP-ILD) ILD [12], the latter being associated with poorer prognosis with mortality rates ranging from 70% to 90% [13–15].

Although corticosteroids and immunosuppressive drugs including methotrexate and azathioprine are the cornerstone of the treatment of IIM muscle associated with rheumatic manifestations [16], no guidelines are available to guide the treatment of IIM-related ILD. We conducted a systematic review and meta-analysis to evaluate the efficacy of the different treatments currently used in the management of both chronic and RP subtypes of IIM-related ILD.

2. Materials and methods

We followed the Meta-Analysis of Observational Studies in Epidemiology guidelines during all the stages of design, implementation and reporting of this meta-analysis [17].

2.1. Study objectives

RP-ILD is generally associated with a rapid decline in lung function and short-term survival is poor, whereas patients with C-ILD is more commonly associated with a progressive decline in pulmonary function. We conducted two meta-analyses to assess the effect of immunosuppressive therapies on IIM-related ILD outcomes. The primary aims of these systematic reviews and meta-analyses were to assess the effects of immunosuppressive therapies on: 1) the survival rates at 3 months amongst patients with RP-ILD and; 2) the proportion of patients with C-ILD who exhibit objectively confirmed improvements on pulmonary function tests. As significant heterogeneity in the definition of significant improvements was expected, we chose to consider the definition used in each study for C-ILD improvement.

2.2. Data sources and searches

An exhaustive literature search, both computer-assisted and manual was performed. The computer-assisted search was conducted on the MEDLINE database up to July 2017 (see search strategy in Appendix).

Table 1
Characteristic of studies reported outcome in chronic interstitial lung disease.

Study	Population	Mean age	Sex (M/F)	Evaluation criteria	Main treatment	Treatment protocol
Marie, 2002‡	DM/PM	54	16/20	PFT	CsA, CYC, AZA	NA
Takada, 2005	PM/DM	49	8/29	PFT	CsA	NA
Wilkes, 2005‡	ARS	45	5/8	PFT	Tacrolimus	Oral, twice daily (0.075 mg/kg) to achieve plasma trough concentration of 5-20 ng/mL
Yamasaki, 2006	PM/DM	51	4/13	PFT	CYC	500–1000 mg (300–800 mg/m^2 every 4 weeks (6 doses) i.v.
Ideura, 2007	ADM	46	5/13	PFT and HRCT	CS alone, CsA	NA
Sem, 2009	ARS	60	4/7	ATS criteria	Rituximab	1000 mg, at days 0 and 14 (9 patients) 375 mg/m^2/week for 4 weeks (2 patients)
Marie, 2010	PM/Scl antibodies	NA	NA	ATS criteria	CS alone, AZA, CYC	NA
Koreeda, 2010	ARS	59	7/7	ATS criteria	CsA	3 mg/kg/day then adjusted to target the trough level (100–200 ng/mL).
Ingegnoli, 2011	ARS (anti-Jo1)	53	0/15	HRCT	CYC, CsA, CS alone	Seven of the 15 patients were treated with oral cyclosporin A (CsA) 5 mg/kg/day and eight with cyclophosphamide (CYC) pulses (1000 mg/m^2 of body surface) monthly for 6 months followed by 3-monthly maintenance pulses
Marie, 2011	PM/DM	53	43/64	ATS criteria	CS alone, CYC, AZA, MMF	NA
Marie, 2012	ARS	57	3/4	ATS criteria	Rituximab	2 infusions of 1 g at days 0 and 14, third infusion of 1 g at 6-month follow-up
Keir, 2012	PM/DM	49	3/2	PFT	Rituximab	2 infusions of 1 g at days 0 and 14
Labirua-Iturburu, 2013	ARS	42	4/11	ATS criteria	CsA, Tacrolimus	Tacrolimus: oral, twice daily 0.065 mg/kg. Cyclosporine: oral, twice daily 2–5 mg/kg.
Marie, 2013‡	ARS (anti-PL7)	60	7/8	ATS criteria	CS alone, AZA, CYC	CS 1 mg/kg/day AZA 2 mg/kg/day CYC 0.7 g/m^2/month (6 pulses) MMF (30 mg/kg/day).
Marie, 2013‡	ARS (anti-Jo1)	55	25/41	ATS criteria	CS alone, AZA, CYC	CS 1 mg/kg/day AZA 2 mg/kg/day CYC 0.7 g/m^2/month (6 pulses) MMF (30 mg/kg/day)

ARS: anti-tRNA synthetase syndrome; AZA: azathioprine; CADM: clinically amyopathic dermatomyositis; CsA: cyclosporine A; CS: corticosteroids; CYC: cyclophosphamide; DM: dermatomyositis.
ATS Criteria: according to an international consensus statement of the American Thoracic Society on idiopathic pulmonary fibrosis, increases of > 10% in FVC and/or > 15%in DLCO were considered to be significant, and were used as determinants of improvement. Deterioration was defined as when any of the features of pulmonary condition worsened despite institution of therapy; decreases of > 10% in FVC and/or > 15% in DLCO were considered significant, and were used as determinant of deterioration.
‡ Consecutive patients.

2.3. Study selection

Inclusion criteria were defined a priori. Searches were restricted to articles published in English or French. Randomized controlled trials, series, case-control and cohort studies were included in the systematic review if: 1) they included adult patients presenting with ILD related to IIM treated either with corticosteroids or immunosuppressive therapies; 2) they reported one of the primary and secondary outcomes of interest. There was no restriction in study design. If available, the diagnosis of IIM was based on Peter and Bohan's criteria (dermatomyositis and polymyositis) and Sontheimer criteria (clinically amyopathic dermatomyositis) [18]. The diagnosis of anti-tRNA synthetase syndrome was based on the presence of an anti-synthetase antibody in patients with ILD.

2.4. Data extraction and quality assessment

Data from eligible studies were independently extracted by two authors (T.B. and R.F.). In case of discrepancy, a consensus was reached. The extracted study characteristics included year of publication, study design (prospective or retrospective), baseline demographical, clinical, and serological data, ILD subtype (chronic or RP), treatments, and outcomes.

2.5. Data synthesis and analysis

The primary assessment criterion was the improvement rate for C-ILD and the 3-month global survival for RP-ILD, expressed as their mean rates, together with their 95% confidence interval (95%CI). We pooled all the studies in a first global analysis of the primary assessment criterion for C-ILD and RP-ILD. We then estimated the efficacy of each treatment in subgroup analyses by calculating the weighted mean proportions. The random-effects model was used in case of heterogeneity. The percentage of variability beyond chance was estimated using the I^2 statistic [19,20]. An I^2 statistic value > 50% indicated substantial heterogeneity. To explain heterogeneity, the effects of covariates (age, IIM subtype, design, year of publication, administrated dose) on response rate were investigated using logarithmic mixed-effects meta-regressions. The risk of publication bias was determined by funnel plot and one-tailed Egger's test [21]. A *p*-value below 0.05 was considered statistically significant in all analyses. We used the plogit transformation for meta-analyzing raw proportions with continuity correction of 0.5 in studies with zero cell frequencies. In practice, such cases were handled by adding 0.5 to the data. All analyses were performed using R software (package meta, version 4.8.1).

3. Results

3.1. Study selection

The flow diagram of the search is depicted in Fig. 1. A total of 1377 studies were identified through electronic databases. Removing irrelevant studies based on title and abstract review reduced the results to 186 records. A total of 27 studies were finally included in the meta-analysis totalizing 553 patients.

Table 2
Characteristic of studies reported outcome in rapidly progressive interstitial lung disease.

Study	Population	Mean age	Sex (M/F)	Evaluation criteria	Main treatment	Treatment protocol
Miyake, 2002	DM	55	3/7	Survival	CsA	Oral, daily adjusted to reach trough levels ranging from 100 to 200 ng/mL
Schnabel, 2003[*,‡]	PM/DM	53	4/16	Survival	CYC	500 mg/m^2 i.v. every 3 weeks with a single dose of 100 mg prednisolone
Takada, 2005	PM/DM	49	8/29	Survival	CsA	NA
Kameda, 2005[*]	DM, CADM, PM	49	2/8	Survival	CS plus CsA plus CYC	CS > 0.5 mg/kg/day prednisolone CYC (i.v.) 10–30 mg/kg every 3–4 weeks CsA 2–4 mg/kg to achieve a trough level of 150–250 ng/mL.
Ideura, 2007	ADM	46	5/13	Survival	CS alone, CsA	NA
Tillie-Leblond, 2008	ARS	NA	NA	Survival	CS alone	NA
Kotani, 2008	DM	59	4/12	Survival	CsA, CYC	Group A: 7 of the 16 patients with DM-A/SIP were treated initially with 1 mg/kg/day prednisolone. When IP was progressive despite the initial treatment, CsA treatment was added. Group B: 9/16 patients were treated initially with 1 mg/kg/day prednisolone plus 4 mg/kg/day CsA.
Mukae, 2009	DM, CADM	62	0/2	Survival	CS alone	NA
Sem, 2009	ARS	60	4/7	Survival	Rituximab	1000 mg, at days 0 and 14 (9 patients) 375 mg/m^2/week for 4 weeks (2 patients)
Suzuki, 2009	PM/ADM	63	2/3	Survival	IVIG	0.4 g/kg/day for 5 days consecutively
Kotani, 2011	DM	54	3/11	Survival	CsA	4 mg/kg/day (oral)
Marie, 2011	PM/DM	53	43/64	Survival	CS alone, CYC, AZA, MMF	NA
Cavagna, 2013	ARS (anti-Jo1)	57	4/13	Survival	CsA	Oral, 3 mg/kg/day
Chen, 2013	DM	52	0/14	Survival	Infliximab	5 mg/kg/week i.v., at week 0, 2, 6 and every 8 weeks
Isoda, 2014	DM	58.6	6/24	Survival	CsA	Oral, once daily, 3.5–4.5 mg/kg/day
Go, 2016	DM/CADM	48	12/35	Survival	CsA	Oral (except 3 i.v. administration) average 160 mg/day

ARS: anti-tRNA synthetase syndrome; AZA: azathioprine; CADM: clinically amyopathic dermatomyositis; CsA: cyclosporine A; CS: corticosteroids; CYC: cyclophosphamide; DM: dermatomyositis.
‡ Consecutive patients.
* Prospective studies.

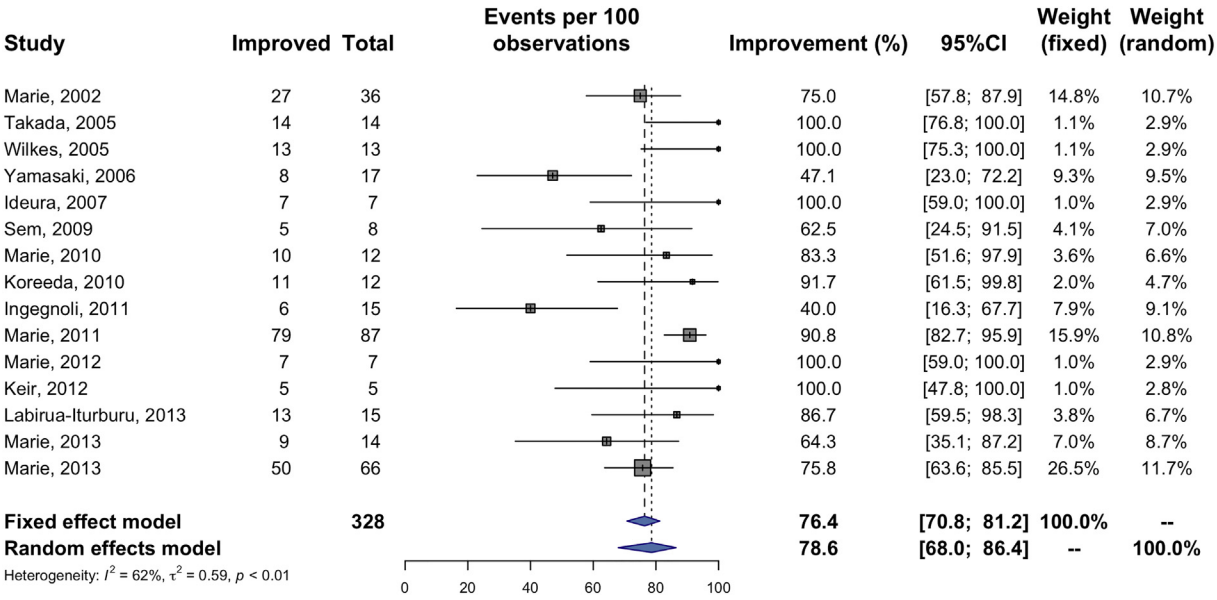

Fig. 2. Global analysis of chronic ILD studies (Forest plot).

3.2. Description of the studies

The main characteristics of the studies are summarized in Tables 1 and 2. A total of 225 patients with RP-ILD (16 studies) and 328 patients with C-ILD (15 studies) were included in the meta-analyses. These studies evaluated the effects of corticosteroids alone (9 studies) or in combination with cyclosporine A (14 studies), tacrolimus (2 studies), azathioprine (4 studies), cyclophosphamide (9 studies), IVIG (1 study) and rituximab (4 studies). Two studies evaluated the efficacy of corticosteroids in association with cyclosporine A and intravenous cyclophosphamide [22]. The studies were performed in Japan (n = 11) [22–32], France (n = 7) [33–39], Italy (n = 2) [40,41], and others (n = 7) [42–48]. Sample size varied from 2 to 87 (mean age = 53.5 ± 5.5, mean male proportion = 30.5%). The ILD was associated with dermatomyositis, polymyositis or clinically amyopathic dermatomyositis in 222, 183 and 85 patients, respectively. Twelve studies focused on anti-tRNA synthetase syndrome (n = 250 patients). For C-ILD, significant improvements were defined using the American Thoracic Society criteria for idiopathic pulmonary fibrosis evaluation (decreases or increases of > 10% in FVC and/or > 15%in DLCO) [49]

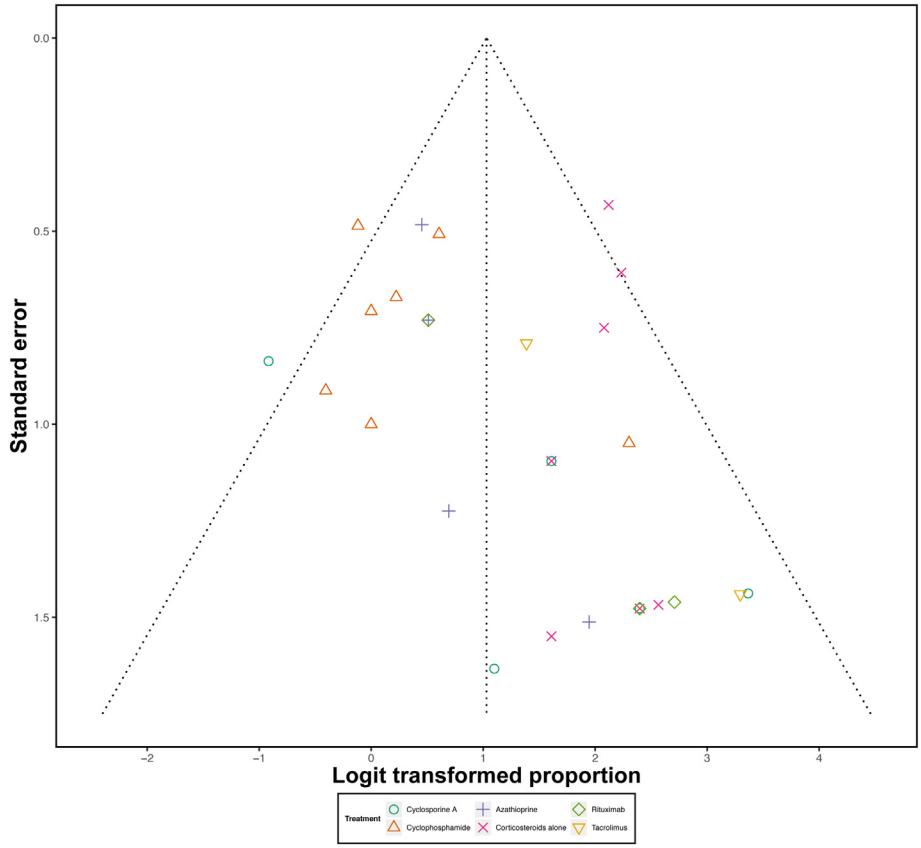

Fig. 3. Funnel plot of chronic ILD studies.

in 9 (33%) studies, whereas other pulmonary functional test criteria were used in 6 studies and high resolution computed tomography in 1 study.

Studies were either prospective (n = 2) [22,43] or retrospective (n = 25) [23–42,44–48] case series. Five studies [24,32,33,38,43,50] included consecutive patients. Individual data were provided in 18 studies (n = 198 patients) [23,25–28,30,37,40,42–44,46–48,51,52]. All the included studies had a high risk of bias.

3.3. Chronic interstitial lung disease

3.3.1. Global analysis

The global improvement rate was evaluated in 15 studies involving 328C-ILD patients. The improvement rate was estimated at 78.6% (95%CI 68.0–86.4) with significant heterogeneity (I^2 = 62%). The global forest plot of C-ILD studies is shown in Fig. 2. The funnel plot of C-ILD studies is depicted in Fig. 3. The Egger's test and the visual inspection of the funnel plot permitted to rule out publication bias (p = 0.24).

3.3.2. Subgroup analyses

The forest plot for the subgroup analyses of studies evaluating corticosteroids alone (n = 7, 124 patients) [26,33–35,38,50,51], cyclosporine A (n = 6, 38 patients) [24,26,33,40,46,51], cyclophosphamide (n = 7, 71 patients) [25,33–35,38,40,50], azathioprine given daily at 2 mg/kg/day (n = 4, 32 patients) [33,34,38,50], tacrolimus given twice daily (0.065–0.075 mg/kg) (n = 2, 23 patients) [46,47] and rituximab intravenously in two 1000 mg pulses at day 0 and day 14 (n = 3, 20 patients) [37,44,48] are shown in Fig. 4. Data about treatment were lacking for 20 patients in one study [35]. Corticosteroids alone, cyclosporine A, cyclophosphamide, azathioprine tacrolimus and rituximab were associated with improvement rates of 89.2% (95%CI 89.2–93.6), 80.7% (95%CI 49.6–94.7), 56.4% (95%CI 44.0–68.0), 64.1% (95%CI 46.3–78.7), 86.2% (95%CI 61.5–96.0%) and 76.6% (95%CI 50.4–91.4), respectively, without heterogeneity except for cyclosporine A (I^2 = 50%, p = 0.07).

3.4. Rapidly progressive interstitial lung disease

3.4.1. Global analysis

The 3-month survival rate was evaluated in 16 studies involving 225 RP-ILD patients. The global 3-month survival rate was estimated at 67.7% (95%CI 60.6–74.0) without significant heterogeneity (I^2 = 41%). The global forest plot of RP-ILD studies is shown in Fig. 5. The funnel plot of RP-ILD studies is depicted in Fig. 6. The Egger's test and the visual inspection permitted to rule out publication bias (p = 0.49).

3.4.2. Subgroup analyses

The forest plot for the subgroup analyses are shown in Fig. 7. Data about treatment were lacking for 11 patients in one study [35]. The efficacy of corticosteroids as a single treatment (n = 2, 11 patients) [32,36], cyclosporine A (n = 8, 146 patients) [23,24,26,30,31,45,52,53], cyclophosphamide (n = 2, 19 patients) [35,43], rituximab (n = 1, 3 patients) [44], intravenous immunoglobulins (n = 1, 5 patients) [28], infliximab (n = 1, 14 patients) [42] and corticosteroids with cyclophosphamide and cyclosporine A (n = 2, 16 patients) [53,54] were assessed. The 3 month rates were 51.7% (95%CI 24.2–78.1), 69.2% (95%CI 55.0–80.5), 72.4% (95%CI 6.4–99.0), 66% (2/3 patients), 40% (2/5), 92.9% (95%CI 63.0–99.0) and 56% (95%CI 31.9–77.6) for corticosteroids alone, cyclosporine A, cyclophosphamide, rituximab, intravenous immunoglobulins, infliximab and the combination of corticosteroids with cyclophosphamide and cyclosporine, respectively, without heterogeneity except for

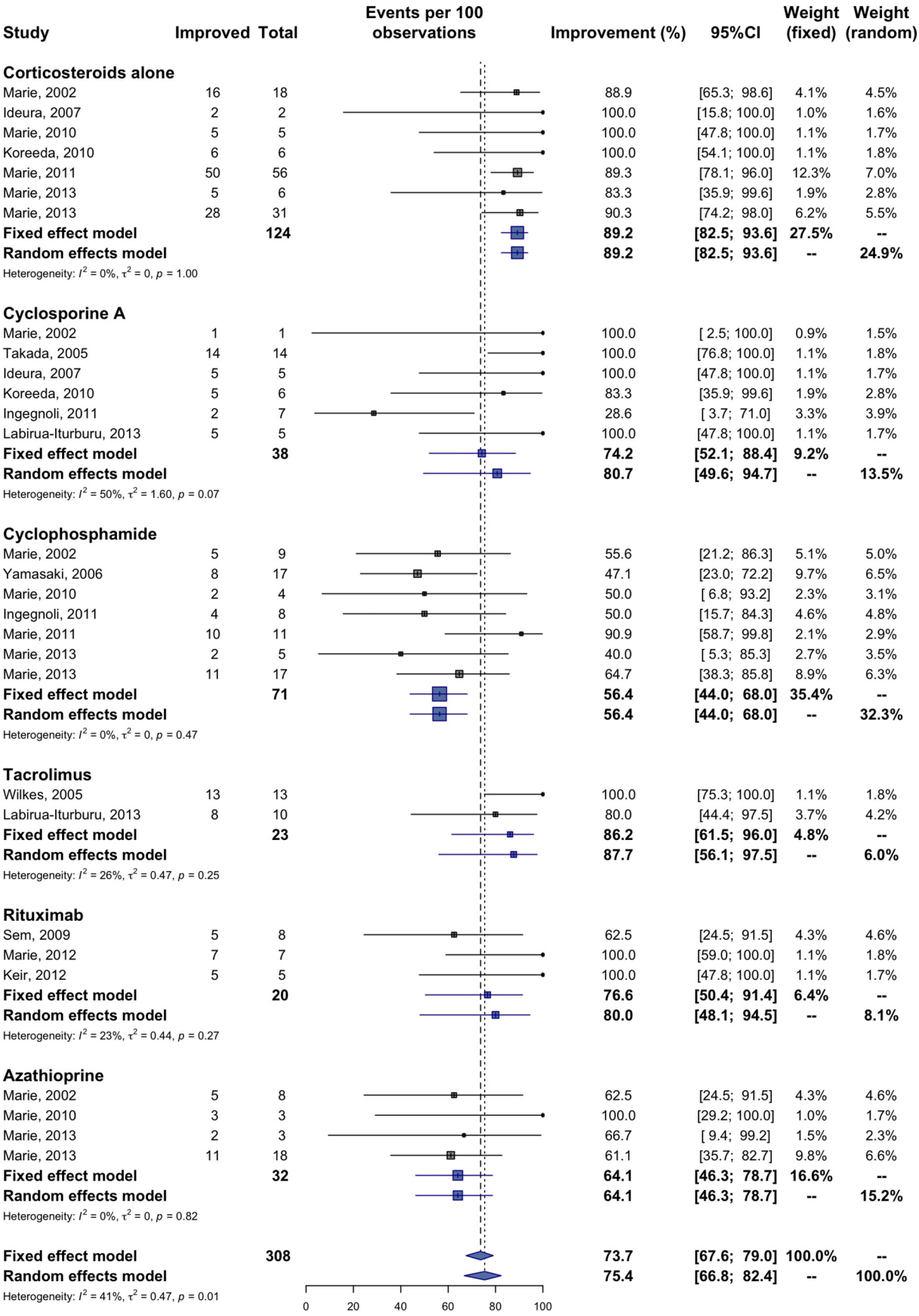

Fig. 4. Subgroup analyses of chronic ILD studies (Forest plot).

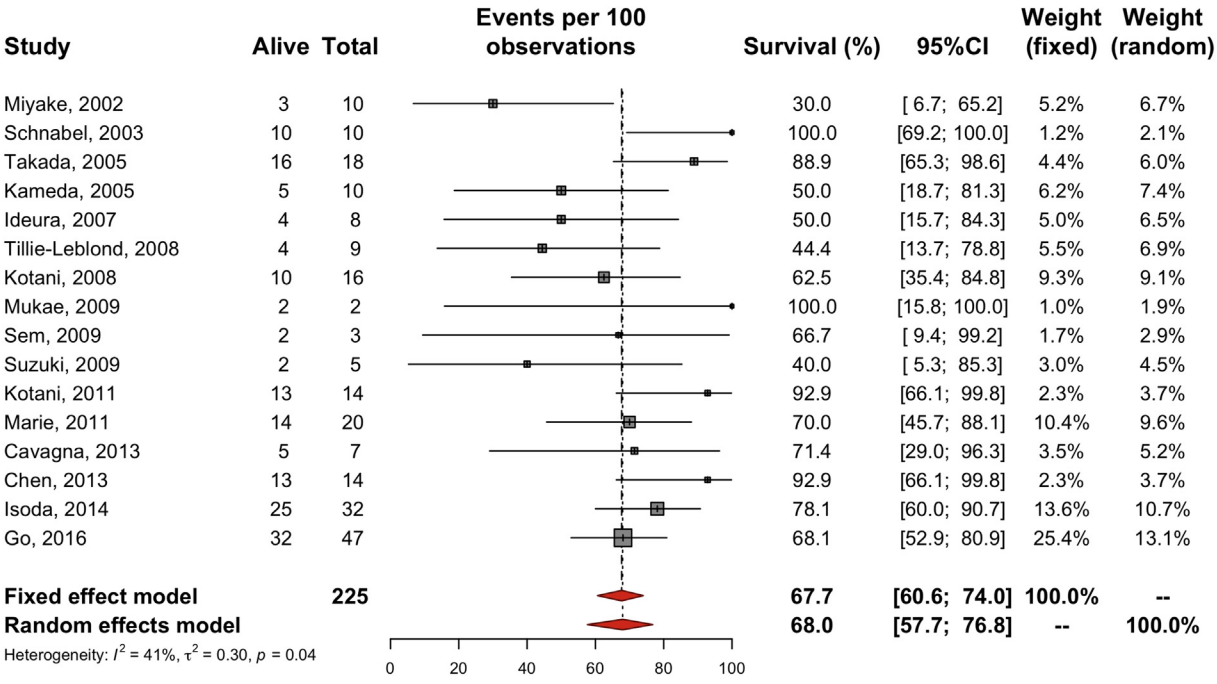

Fig. 5. Global analysis of rapidly progressive ILD studies (Forest plot).

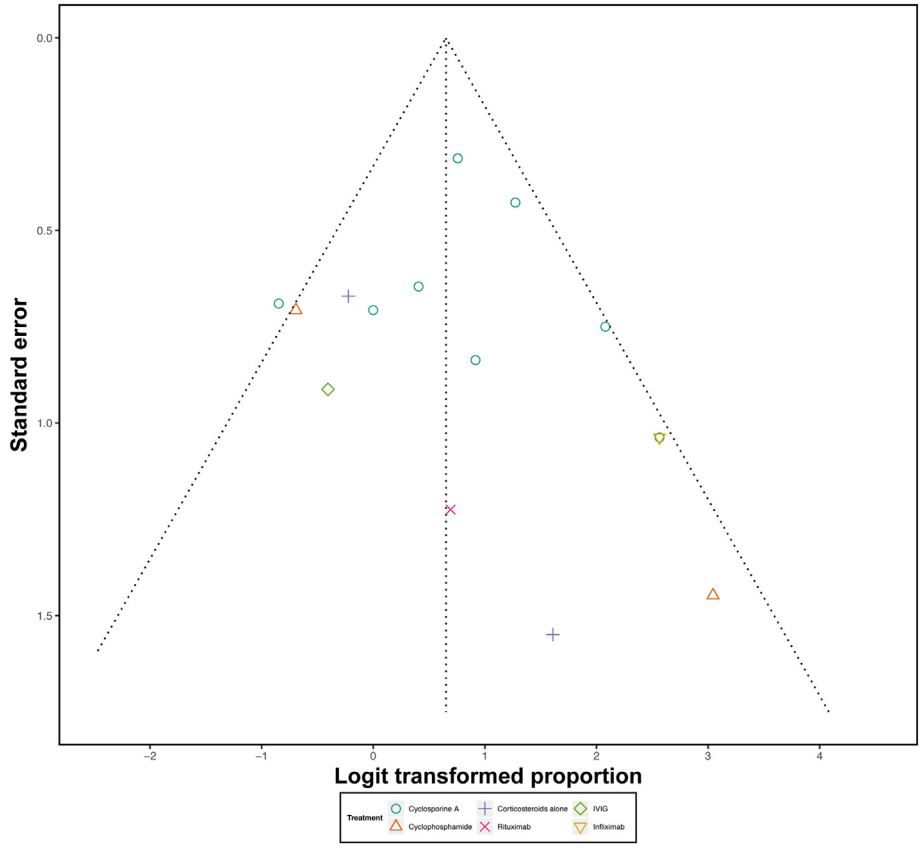

Fig. 6. Funnel plot of rapidly progressive ILD studies.

cyclosporine A (I^2 = 51%, p = 0.04) and cyclophosphamide (I^2 = 81%, p = 0.02).

4. Discussion

Establishing an optimal management of IIM associated ILD is a difficult task, due to i) the low prevalence of the disease, ii) the high variability in the disease presentation, and iii) the absence of consensual criteria for the assessment of treatment efficacy amongst published series. Therefore, the management of IIM-associated ILD today relies upon corticosteroids and immunosuppressive drugs, with no consensus or priority of one treatment over the others.

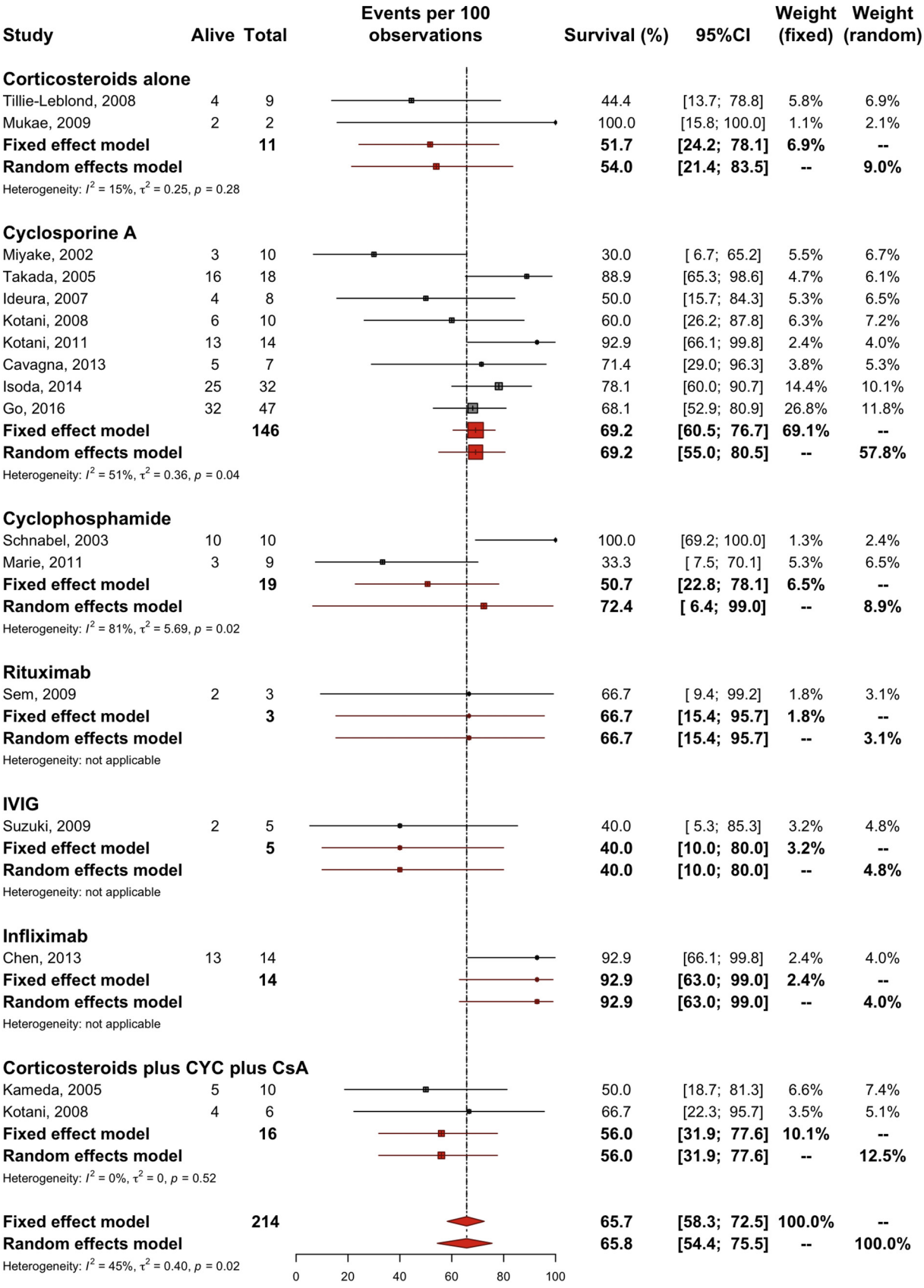

Fig. 7. Subgroup analyses of rapidly progressive ILD studies (Forest plot).

Our meta-analysis reported > 80% efficacy of corticosteroids alone in the management of IIM-associated C-ILD. However, these apparent good results are likely biased, common practice encouraging to treat minor diseases with corticosteroids alone and reserve immunosuppressive drugs for more severe or steroid-resistant ILD, or for patients expected to poorly tolerate corticosteroids due to comorbidities, especially diabetes or osteoporosis. Nevertheless, our results advocate for the use of corticosteroids alone as first line for the induction of C-ILD in patients without significant comorbidities. Second-line immunosuppressants, used in association with corticosteroids, were found to be moderately effective in the management of C-ILD, with a similar treatment effect (i.e. around three quarter of improvement) for cyclosporine A, azathioprine, rituximab and tacrolimus. This apparent effect of therapies targeting various immunological pathways (i.e. T cell activation with calcineurin inhibitors, and B cells with rituximab) may witness the heterogeneity that is observed in the clinical spectrum of IIM. In the absence of controlled studies, however, the present meta-analysis did not allow to draw firm conclusions differential efficacy of these specific therapies. Hence, cyclophosphamide, often administrated as a third-line therapy or in more severe diseases [27,43], was effective in half of the cases, which is lower than second-line immunosuppressants and likely representative of the poorer outcomes of refractory cases.

In RP-ILD, the survival with corticosteroids is much lower with response rates of 50%, which justifies the requirement to additional immunosuppressive therapy [32,36]. Published data concerning RP-ILD are scarcer and mainly concern cyclosporine A and, to a lesser extent, cyclophosphamide and infliximab. The survival rates were disappointingly low (about two third of survivors at 3 months), which denotes an urgent need for randomized trials testing alternative strategies in the management of RP-ILD including combined immunosuppressive therapies [22]. Two studies focused on the combination of immunosuppressive regimens [53,54]. Kameda et al. [22] conducted a pilot trial in which Japanese RP-ILD patients received a combined immunosuppressive therapy with high-dose corticosteroids, intravenous cyclophosphamide, altogether with oral cyclosporine A. The survival rate for the enrolled patients was of 50% in comparison with 25% with conventional therapy (high dose prednisolone plus cyclosporine A or cyclophosphamide or azathioprine). Moreover, deaths were attributed to respiratory failure rather than adverse events, suggesting that some patients may benefit from an association of immunosuppressants. Unfortunately, no prognosis marker is currently validated to identify the subgroup of patients at highest risk of death.

This meta-analysis also underlines the potential efficacy of cyclosporine A and tacrolimus in the management of chronic presentations of IIM-associated C-ILD. Cyclosporine A and tacrolimus are a calcineurin inhibitors targeting T cell activation. Scientific reports justify the targeting of T cells during anti-tRNA synthetase syndrome by the fact that anti-Jo1 autoreactive T cells play a key role in the appearance of ILD in murine models of disease [55]. Interestingly, while the former is most commonly used, tacrolimus appears as effective as cyclosporine A in the present meta-analysis, although the number of studies was very limited. This comforts a potential role of T cell activation in the pathogenesis of IIM-associated ILD and encourages for more specialized trials to assess the efficacy calcineurin inhibitors in these diseases, especially as the use of cyclosporine A is limited by the endothelial and renal toxicity (which is potentially lethal). Moreover, published experiences with cyclosporine A largely emanate from series in Asia, with much more limited experience in European and American centers. Moreover, the risk–benefit ratio and the appropriate positioning of this drug in the treatment algorithm are still unclear. Of note, cyclophosphamide, which is the most potent immunosuppressive drug of our armamentarium, appears less effective than calcineurin inhibitors in C-ILD, although this may be related to selection bias.

Our study suffers from substantial limitations, essentially related to the design and heterogeneity between the included studies. Because of the low number of studies and available data, we could not explore heterogeneity by metaregression but the main reasons for this heterogeneity are easily identifiable. The first cause of heterogeneity is the extreme variability of the clinical presentations of both ILD and IMM. Moreover, most of studies used old IIM classification despite of the proposal of new criteria based on muscle histopathology and the discovery of numerous myositis specific autoantibodies including anti-MDA5. We decided to gather the subgroups according to the clinical course of the disease (C– or RP-ILD) because this dichotomy seemed more relevant in terms of prognosis, but we cannot rule out heterogeneity in the underlying IIM, including the circulating auto-antibodies (e.g. anti-MDA5 antibodies more often associated with RP-ILD). The second cause of heterogeneity is likely partially related to the different evaluation criteria of efficacy. Most of the studies however used the composite American Thoracic Society criteria established for the management of idiopathic pulmonary fibrosis, which relies on functional tests, and is accurately transposable to our problematic. Furthermore, retrospective design of the included studies, corresponding mainly to non-consecutive series, constitutes another significant limitation. Scarce data were also available concerning adverse effects occurring during the follow-up; thus the benefit-risk ratio is difficult to be established, especially for C-ILD. Moreover, a non-negligible number of studies were excluded from the analysis because they lacked therapeutic data, particularly data about concomitant treatments.

In conclusion, these meta-analyses advocate for the use of corticosteroids alone as first line treatment of C-ILD and corticosteroids in association with other immunosuppressive drugs in the management of RP-ILD. Prospective studies and randomized controlled trials are needed to precisely determine the efficacy of these drugs in the management of these severe diseases.

References

[1] Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet 2003;362:971–82.
[2] Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344–7.
[3] Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med 1975;292:403–7.
[4] Mahler M, Miller FW, Fritzler MJ. Idiopathic inflammatory myopathies and the anti-synthetase syndrome: a comprehensive review. Autoimmun Rev 2014;13:367–71.
[5] Cottin V, Thivolet-Bejui F, Reynaud-Gaubert M, Cadranel J, Delaval P, Ternamian P-J, et al. Interstitial lung disease in amyopathic dermatomyositis, dermatomyositis and polymyositis. Eur Respir J 2003;22:245–50.
[6] Saketkoo LA, Ascherman DP, Cottin V, Christopher-Stine L, Danoff SK, Oddis CV. Interstitial lung disease in idiopathic inflammatory myopathy. Curr Rheumatol Rev 2010;6:108–19.
[7] Lega JC, Fabien N, Reynaud Q, Durieu I, Durupt S, Dutertre M, et al. The clinical phenotype associated with myositis-specific and associated autoantibodies: a meta-analysis revisiting the so-called antisynthetase syndrome. Autoimmun Rev 2014;13:883–91.
[8] Sato S, Hirakata M, Kuwana M, Suwa A, Inada S, Mimori T, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum 2005;52:1571–6.
[9] Wolfe JF, Adelstein E, Sharp GC. Antinuclear antibody with distinct specificity for polymyositis. J Clin Invest 1977;59:176–8.
[10] Lega JC, Cottin V, Fabien N, Thivolet-Bejui F, Cordier JF. Interstitial lung disease associated with anti-PM/Scl or anti-aminoacyl-tRNA synthetase autoantibodies: a similar condition? J Rheumatol 2010;37:1000–9.
[11] Troyanov Y, Targoff IN, Payette MP, Raynauld JP, Chartier S, Goulet JR, et al. Redefining dermatomyositis: a description of new diagnostic criteria that differentiate pure dermatomyositis from overlap myositis with dermatomyositis features. Medicine (Baltimore) 2014;93:318–32.
[12] Ye S, Chen XX, Lu XY, Wu MF, Deng Y, Huang WQ, et al. Adult clinically amyopathic dermatomyositis with rapid progressive interstitial lung disease: a retrospective cohort study. Clin Rheumatol 2007;26:1647–54.
[13] Kobayashi N, Takezaki S, Kobayashi I, Iwata N, Mori M, Nagai K, et al. Clinical and laboratory features of fatal rapidly progressive interstitial lung disease associated with juvenile dermatomyositis. Rheumatology (Oxford) 2015;54:784–91.
[14] Xu Y, Yang CS, Li YJ, Liu XD, Wang JN, Zhao Q, et al. Predictive factors of rapidly progressive-interstitial lung disease in patients with clinically amyopathic dermatomyositis. Clin Rheumatol 2016;35:113–6.
[15] Lega JC, Reynaud Q, Belot A, Fabien N, Durieu I, Cottin V. Idiopathic inflammatory myopathies and the lung. Eur Respir Rev 2015;24:216–38.
[16] Jones J, Wortmann R. Idiopathic inflammatory myopathies-a review. Clin

Rheumatol 2015;34:839–44.
[17] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
[18] Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis sine myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? J Am Acad Dermatol 2002;46:626–36.
[19] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
[20] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[21] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[22] Kameda H, Nagasawa H, Ogawa H, Sekiguchi N, Takei H, Tokuhira M, et al. Combination therapy with corticosteroids, cyclosporin A, and intravenous pulse cyclophosphamide for acute/subacute interstitial pneumonia in patients with dermatomyositis. J Rheumatol 2005;32:1719–26.
[23] Miyake S, Ohtani Y, Sawada M, Inase N, Miyazaki Y, Takano S, et al. Usefulness of cyclosporine A on rapidly progressive interstitial pneumonia in dermatomyositis. Sarcoidosis Vasc Diffuse Lung Dis 2002;19:128–33.
[24] Takada K, Nagasaka K, Miyasaka N. Polymyositis/dermatomyositis and interstitial lung disease: a new therapeutic approach with T-cell-specific immunosuppressants. Autoimmunity 2005;38:383–92.
[25] Yamasaki Y, Yamada H, Yamasaki M, Ohkubo M, Azuma K, Matsuoka S, et al. Intravenous cyclophosphamide therapy for progressive interstitial pneumonia in patients with polymyositis/dermatomyositis. Rheumatology 2007;46:124–30.
[26] Ideura G, Hanaoka M, Koizumi T, Fujimoto K, Shimojima Y, Ishii W, et al. Interstitial lung disease associated with amyopathic dermatomyositis: review of 18 cases. Respir Med 2007;101:1406–11.
[27] Kotani T, Makino S, Takeuchi T, Kagitani M, Shoda T, Hata A, et al. Early intervention with corticosteroids and cyclosporin A and 2-hour postdose blood concentration monitoring improves the prognosis of acute/subacute interstitial pneumonia in dermatomyositis. J Rheumatol 2008;35:254–9.
[28] Suzuki Y, Hayakawa H, Miwa S, Shirai M, Fujii M, Gemma H, et al. Intravenous immunoglobulin therapy for refractory interstitial lung disease associated with polymyositis/dermatomyositis. Lung 2009;187:201–6.
[29] Koreeda Y, Higashimoto I, Yamamoto M, Takahashi M, Kaji K, Fujimoto M, et al. Clinical and pathological findings of interstitial lung disease patients with anti-aminoacyl-tRNA synthetase autoantibodies. Intern Med 2010;49:361–9.
[30] Kotani T, Takeuchi T, Makino S, Hata K, Yoshida S, Nagai K, et al. Combination with corticosteroids and cyclosporin-A improves pulmonary function test results and chest HRCT findings in dermatomyositis patients with acute/subacute interstitial pneumonia. Clin Rheumatol 2011;30:1021–8.
[31] Isoda K, Takeuchi T, Kotani T, Hata K, Shoda T, Ishida T, et al. Pre-treatment ferritin level and alveolar-arterial oxygen gradient can predict mortality rate due to acute/subacute interstitial pneumonia in dermatomyositis treated by cyclosporine a/glucocorticosteroid combination therapy: a case control study. PloS One 2014;9.
[32] Mukae H. Clinical differences between interstitial lung disease associated with clinically amyopathic dermatomyositis and classic dermatomyositis. Chest J 2009;136:1341.
[33] Marie I, Hachulla E, Cherin P, Dominique S, Hatron PY, Hellot MF, et al. Interstitial lung disease in polymyositis and dermatomyositis. Arthritis Rheum 2002;47:614–22.
[34] Marie I, Lahaxe L, Benveniste O, Delavigne K, Adoue D, Mouthon L, et al. Long-term outcome of patients with polymyositis/ dermatomyositis and anti-PM-Scl antibody. Br J Dermatol 2010;162:337–44.
[35] Marie I, Hatron PY, Dominique S, Cherin P, Mouthon L, Menard J-F. Short-term and long-term outcomes of interstitial lung disease in polymyositis and dermatomyositis: a series of 107 patients. Arthritis Rheum 2011;63:3439–47.
[36] Tillie-Leblond I, Wislez M, Valeyre D, Crestani B, Rabbat A, Israel-Biet D, et al. Interstitial lung disease and anti-Jo-1 antibodies: difference between acute and gradual onset. Thorax 2008;63:53–9.
[37] Marie I, Dominique S, Janvresse A, Levesque H, Menard J-F. Rituximab therapy for refractory interstitial lung disease related to antisynthetase syndrome. Respir Med 2012;106:581–7.
[38] Marie I, Josse S, Decaux O, Diot E, Landron C, Roblot P, et al. Clinical manifestations and outcome of anti-PL7 positive patients with antisynthetase syndrome. Eur J Intern Med 2013;24:474–9.
[39] Marie I, Josse S, Hatron PY, Dominique S, Hachulla E, Janvresse A, et al. Interstitial lung disease in anti-Jo-1 patients with antisynthetase syndrome. Arthritis Care Res 2013;65:800–8.
[40] Ingegnoli F, Lubatti C, Ingegnoli A, Boracchi P, Zeni S, Meroni PL. Interstitial lung disease outcomes by high-resolution computed tomography (HRCT) in Anti-Jo1 antibody-positive polymyositis patients: a single centre study and review of the literature. Autoimmun Rev 2012;11:335–40.
[41] Cavagna L, Caporali R, Abdi-Ali L, Dore R, Meloni F, Montecucco C. Cyclosporine in anti-Jo1-positive patients with corticosteroid-refractory interstitial lung disease. J Rheumatol 2013;40:484–92.
[42] Chen D, X-B Wang, Zhou Y, X-C Zhu. Efficacy of infliximab in the treatment for dermatomyositis with acute interstitial pneumonia: a study of fourteen cases and literature review. Rheumatol Int 2013;33:2455–8.
[43] Schnabel A, Reuter M, Biederer J, Richter C, Gross WL. Interstitial lung disease in polymyositis and dermatomyositis: clinical course and response to treatment. Semin Arthritis Rheum 2003;32:273–84.
[44] Sem M, Molberg O, Lund MB, Gran JT. Rituximab treatment of the anti-synthetase syndrome—a retrospective case series. Rheumatology 2009;48:968–71.
[45] Go DJ, Park JK, Kang EH, Kwon HM, Lee YJ, Song YW, et al. Survival benefit associated with early cyclosporine treatment for dermatomyositis-associated interstitial lung disease. Rheumatol Int 2016;36:125–31.
[46] Labirua-Iturburu A, Selva-O'Callaghan A, Martinez-Gomez X, Trallero-Araguas E, Labrador-Horrillo M, Vilardell-Tarres M. Calcineurin inhibitors in a cohort of patients with antisynthetase-associated interstitial lung disease. Clin Exp Rheumatol 2013;31:436–9.
[47] Wilkes MR, Sereika SM, Fertig N, Lucas MR, Oddis CV. Treatment of antisynthetase-associated interstitial lung disease with tacrolimus. Arthritis Rheum 2005;52:2439–46.
[48] Keir GJ, Maher TM, Hansell DM, Denton CP, Ong VH, Singh S, et al. Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy. Eur Respir J 2012;40:641–8.
[49] Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788–824.
[50] Marie I, Josse S, Hatron PY, Dominique S, Hachulla E, Janvresse A, et al. Interstitial lung disease in anti-Jo-1 patients with antisynthetase syndrome: ILD in anti-Jo-1 patients. Arthritis Care Res 2013;65:800–8.
[51] Koreeda Y, Higashimoto I, Yamamoto M, Takahashi M, Kaji K, Fujimoto M, et al. Clinical and pathological findings of interstitial lung disease patients with anti-aminoacyl-tRNA synthetase autoantibodies. Intern Med 2010;49:361–9.
[52] Cavagna L, Caporali R, Abdi-Ali L, Dore R, Meloni F, Montecucco C. Cyclosporine in anti-Jo1-positive patients with corticosteroid-refractory interstitial lung disease. J Rheumatol 2013;40:484–92.
[53] Kotani T, Makino S, Takeuchi T, Kagitani M, Shoda T, Hata A, et al. Early intervention with corticosteroids and cyclosporin A and 2-hour postdose blood concentration monitoring improves the prognosis of acute/subacute interstitial pneumonia in dermatomyositis. J Rheumatol 2008;35:254–9.
[54] Kameda H, Nagasawa H, Ogawa H, Sekiguchi N, Takei H, Tokuhira M, et al. Combination therapy with corticosteroids, cyclosporin A, and intravenous pulse cyclophosphamide for acute/subacute interstitial pneumonia in patients with dermatomyositis. J Rheumatol 2005;32:1719–26.
[55] Katsumata Y, Ridgway WM, Oriss T, Gu X, Chin D, Wu Y, et al. Species-specific immune responses generated by histidyl-tRNA synthetase immunization are associated with muscle and lung inflammation. J Autoimmun 2007;29:174–86.